REMARKS

Claims 17-27 presently appear in this case. Claims 20-22 and 25 have been withdrawn from consideration, pending allowance of a generic claim. No claims have been allowed. The official action of October 8, 2008, has now been carefully studied. Reconsideration and allowance are hereby respectfully urged.

Briefly, the present invention relates to a process for upregulating T-cell cytokine secretion, T-cell adhesion or T-cell chemotactic migration in a mammalian subject by treating a population of T-cells *ex vivo* with a molecule that causes stimulation of glutamate receptor activation, using an amount of that molecule that is sufficient to stimulate glutamate receptor activation, thereby upregulating such T-cell activity. That treated T-cell population is then administered to the subject. The molecule that causes stimulation of glutamate receptor activation is glutamate, a glutamate analog, an anti-glutamate receptor antibody, or an expressible polynucleotide encoding a glutamate receptor. The analog or the antibody is one that stimulates glutamate receptor activation as measured by upregulation of T-cell cytokine secretion, adhesion, or chemotactic migration.

Reconsideration and withdrawal of the finality of the official action of October 8, 2008, is respectfully urged. The finality is premature because the new art rejection of anticipation by Winter was not necessitated by applicant's amendments to the claims. Claim 6 as originally filed stated that the T-cells are exposed to glutamate *in vitro*. Originally filed claim 14 was directed to administering glutamate to T-cells *ex vivo* and then administering the T-cells to the patient. The Winter reference could and should have been applied with respect to the original claims so that applicant would have had more than one opportunity to respond. Accordingly, as this rejection of the present claims was not necessitated by the amendment to the claims, reconsideration and withdrawal of the finality of the Official Action of October 8, 2008 is respectfully urged.

Claim 26 has been rejected under 35 USC 112, first paragraph, as failing to comply with the written description requirement. The examiner states that this is a new matter rejection. The examiner states that the specification does not support the use of a molecule that stimulates an "ionotropic" glutamate receptor.

The examiner's attention is invited to the paragraph at page 87, beginning at line 12 (the last paragraph of Example 3). The concept of use of a molecule that stimulates an

ionotropic glutamate receptor is supported in this paragraph. It states that glutamate receptors are commonly divided into two major groups, metabotropic and ionotropic. The paragraph then states that an example is provided of an ionotropic glutamate receptor antagonist that is effective. That paragraph concludes:

> The results clearly indicate that Glutamate markedly induces adherence of normal human T-cells to extracellular matrix proteins, mediated by stimulation of previously uncharacterized specific ionotropic lymphocyte Glutamate receptors.

Accordingly, the concept of using a molecule that stimulates ionotropic glutamate receptors is supported by the specification and claim 27 does not contain any new matter. Reconsideration and withdrawal of this rejection is respectfully urged.

Claims 17, 19, 23, 24, 26 and 27 have been rejected under 35 USC 112, first paragraph, as failing to comply with the written description requirement in that there is insufficient written description to demonstrate that applicant was in possession of the claimed genus of Glutamate "analogs." The examiner states that the glutamate receptor exists as a myriad of different subtypes and it is not clear how much identity is "substantial" identify. This rejection is respectfully traversed.

Claim 17(b) requires that the analog be capable of stimulating glutamate receptor activation as measured by upregulation of T-cell cytokine secretion, adhesion or chemotactic migration. Claim 17 has now been amended to delete reference to "substantial degree of structural identity" in order to avoid the indefiniteness noted by the examiner. The point is that all of the five analogs disclosed in the specification stimulate glutamate receptor as measured by upregulation of T-cell cytokine secretion, adhesion or chemotactic migration. Therefore, applicant has many species that support the fact that applicant was in possession of the entire genus. It is irrelevant which subspecies of receptor may be involved in this activation. The point is that glutamate and many specified analogs stimulate activation of at least some glutamate receptors sufficiently to cause the effect required by the claim. The examiner has conceded that it would not take undue experimentation to determine which other glutamate analogs will have these properties. Any given analog can be tested to determine whether or not it has the properties required. Thus, there is no reason to believe that applicant was not in possession of the use of all glutamate analogs that have this property. Reconsideration and withdrawal of this rejection is therefore respectfully urged.

Claims 17-19, 23, 24 and 26-27 have been rejected under 35 USC 112, first paragraph, because the specification, while being enabling for a method for upregulating T-cell cytokine secretion, T-cell adhesion or chemokine mediated migration by stimulating glutamate receptor activation, does not reasonably provide enablement for a method for upregulating T-cell activity by stimulating glutamate receptor activation. This rejection is respectfully traversed.

Claim 17 has now been amended to be directed specifically to the method that the examiner has conceded as being supported by sufficient enabling disclosure, i.e., a method for upregulating T-cell cytokine secretion, T-cell adhesion or T-cell chemokine mediated migration. Accordingly, this rejection has now been obviated.

Claims 17, 18, 23, 24 and 26 to 27 have been rejected under 35 USC 102b as being anticipated by Winter as evidenced by Droge. The examiner states that Winter teaches a method of enhancing the anti-tumor T-cell response by administering T-cells to a subject with a tumor. The examiner states that Winter teaches that the T-cells are cultured *ex vivo* in RPMI medium before administration. The examiner states that, as evidenced by Droge, RPMI medium contains glutamate. Thus, the examiner states that Winter has inherently treated T-cells *ex vivo* with glutamate and such glutamate treatment would

inherently stimulate the glutamate receptor, including the GluR3 receptor. This rejection is respectfully traversed.

The issue raised by the examiner has also been raised in another context previously. Submitted herewith is a page from the *Journal of Immunology* that includes, "Comment on 'TCR Activation Eliminates Glutamate Receptor GluR3 from the Cell Surface of Normal Human T cells, via an Autocrine/Paracrine Granzyme B-Mediated Proteolytic Cleavage'" and "Response to Comment on 'TCR Activation Eliminates Glutamate Receptor GluR3 from the Cell Surface of Normal Human T cells, via an Autocrine/Paracrine Granzyme B-Mediated Proteolytic Cleavage.'" Both of these appear at *J. Immunology* 180:2007 (2008). The comment requested clarification of the use of RPMI 1640 as a culture medium in experiments where the effects of 10nM glutamate were studied. The response from one of the authors (the present inventor) has two explanations for the authors' ability to reliably and repetitively measure the effects of 10nM glutamate. They first speak of the fact that one obtains a bell curve of activity from 10^{-14} - 10^{-4}, as described in Ganor et al., "Human T-cells express a functional ionotropic glutamate receptor GluR3, and glutamate by itself triggers integrin-mediated adhesion of laminin and fibronectin and chemotactic migration," *J. Immunol.* 170:4362-4370 (2003), copy also submitted herewith. The second explanation is linked to the

aging of the RPMI 1640 and to the disappearance of glutamate that originally was present at the unstable concentration of 136 micromolar.

The examiner's attention is invited to Figure 4 of the Ganor paper discussed above. This figure shows a dose response curve for glutamate's effects on T-cells and shows that the curve has a clear bell shape and that the activation of T-cells is obtained only in the 10nM range but not at higher concentrations like those that are present in RPMI. Thus, this dose response data shows that when human T-cells see a very high concentration of glutamate, such as that in RPMI, they do not respond to it as they are "blunt" to this high glutamate concentration. However, when the cells see a low, optimal 10nM glutamate, they respond optimally again as seen in the dose response curve shown at Figure 4.

Claim 17 requires that the T-cells be treated with a molecule that causes stimulation of glutamate receptor activation "in an amount sufficient to stimulate glutamate receptor activation." The amount in RPMI 1640 will not cause stimulation of glutamate receptor activation as it is much too concentrated. The present specification shows that the presence of RPMI 1640 will not prevent the activation of the T-cells by incubation with the preferred concentration of glutamate. Such incubation takes place in solution in PBS and causes activation

of the T-cells, as can be seen by the reliable and repetitively measurable effects of the examples in the present specification. Accordingly, Winter does not anticipate the present invention. Reconsideration and withdrawal of this rejection is respectfully urged.

While it is believed that the finality of the Offical Action of October 8, 2008, should be withdrawn, for the reasons set forth above, even if the finality is not withdrawn, the present amendment should be entered as it only removes issues for the purpose of appeal or places the claims in condition for allowance. No new issues requiring further search or consideration have been presented. Accordingly, entry of the present amendment at least for the purpose of appeal is respectfully urged.

It is submitted that all of the claims now present in the case clearly define over the references of record and fully comply with 35 USC 112. Reconsideration and allowance are therefore earnest solicited.

Respectfully submitted,

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